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Letters to the Editor

Comments on "Anti-Influenza Prodrug Oseltamivir Is Activated by Carboxylesterase Human Carboxylesterase 1, and the Activation Is Inhibited by Antiplatelet Agent Clopidogrel"

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Shi et al. (2006) conclude in their recent article that, because clopidogrel inhibits the hydrolysis and therefore the activation of oseltamivir, the concurrent use of these drugs would render the latter therapeutically inactive. In reaching their conclusions, we believe that the authors have extrapolated their findings beyond the scope of the study and have addressed neither the limitations of their in vitro dataset nor the clinical relevance of the drug concentrations evaluated, as illustrated below.

1) The experimental conditions used in vitro do not reflect the in vivo situation. For oseltamivir, the 50 μM concentration used corresponds to approximately 240 times the maximal plasma concentration obtained with the approved 75-mg twice daily regimen (unpublished observations). For clopidogrel, even the lowest concentration used in the in vitro assessments, at which the Shi et al. (2006) reported approximately 30% reduction in hydrolytic activity, was more than 400-fold greater than the plasma C_{max} of clopidogrel using the standard 75-mg once daily regimen (Slugg et al., 2000). Therefore, there is a considerable margin for the liver concentration to be elevated compared with plasma, with no expectation of a significant interaction taking place, especially if unbound clopidogrel concentrations are considered.

The in vitro assessments are based on static conditions and do not take into account the decay in the plasma concentrations with time. Therefore, the risk of a sustained interaction that might lead to therapeutic failure of oseltamivir is remote when one considers the small time window over which the highest clopidogrel concentrations are experienced in vivo. For example, after a high 600-mg dose of clopidogrel, the C_{max} was 38 ng/ml occurring within 1.4 h after administration, and concentrations rapidly decayed to undetectable levels with a mean ± S.D. half-life of 1 ± (0.5) h.

Furthermore, the assumption, implicit in the described in vitro methodology, is that an increase in oseltamivir prodrug concentrations will equate to a decrease in circulating carboxylate levels by the same percentage. However, this is not relevant to the in vivo situation for the following reason. Because metabolism to the carboxylate is the primary route of clearance for oseltamivir [renal clearance accounts for less than 5% of the dose (He et al, 1999)], a large proportion of the oseltamivir area under the curve will remain to be converted to metabolite once the inhibition by clopidogrel subsides. This supports the view that estimates of the magnitude of increase in exposure to oseltamivir prodrug following concomitant administration with clopidogrel are probably greater than the magnitude of decrease in exposure to the carboxylate.

2) Shi et al. (2006) suggest that the relative concentrations of oseltamivir and clopidogrel are the primary determinant of interaction potential. Although this is partly true, negligible inhibition occurs if concentrations of an inhibitor (clopidogrel) and substrate (oseltamivir) are well below their respective K_i and K_M values, as would be the case using the approved clinical regimens. In fact, the primary driver for an interaction (in this case the magnitude of inhibition) is the relationship between the unbound concentration of the inhibitor (clopidogrel) and the K_i, a routine comparison that Shi et al. (2006) have not made. Citing previous work by Tang et al. (2006), the authors also assert that because clopidogrel is hydrolyzed faster by human carboxylesterase 1 (HCE1) than oseltamivir, clopidogrel is preferentially metabolized by this enzyme. This statement is not relevant to a discussion of the potential for an interaction and confuses the capability of clopidogrel to bind to HCE1 and inhibit oseltamivir hydrolysis (K_i), with the catalytic efficiency of HCE1 for clopidogrel hydrolysis (V_{max}/K_M).

3) Because HCE1 is a liver microsomal enzyme, it would have been reasonable to have used the drug-drug interaction risk assessment procedure recommended by the United States Food & Drug Administration for cytochrome P450 inhibitors (www.fda.gov/cder/guidance/index.htm; United States Food & Drug Administration, 2006), but this was not done. By applying this procedure to the data presented by Shi et al. (2006) and using both the approved 75-mg daily dose and the approved 300-mg loading dose of clopidogrel, the risk of a clinically significant interaction due to clopidogrel inhibition of oseltamivir hydrolysis is judged as remote. Using alternative methods [Ito et al. (1998)] that involve estimation of the unbound inhibitor concentrations at the enzyme level (taking into account the contribution of the systemic circulation and absorption), the same conclusion is reached.

4) Shi et al. (2006) observed reduced viability of transfected

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ABBREVIATIONS: HCE1, human carboxylesterase.

cells expressing HCE1 that were exposed to high concentrations of oseltamivir (up to 320 μM) but did not comment on how relevant these findings were in relation to the usual clinical exposures of oseltamivir (1500-fold less at 0.21 μM). In long-term toxicological studies in rats and monkeys, doses up to 1000 mg/kg oseltamivir were studied. The maximal plasma concentrations of oseltamivir carboxylate in these animals were approximately 65 μg/ml (229 μM) and 93 μg/ml (327 μM), respectively. Despite these high exposures, no cytotoxicity was found (unpublished observations).

5) Finally, as part of their argument for HCE1 being wholly responsible for the hydrolytic transformation of oseltamivir, Shi et al. (2006) cited pharmacokinetic studies in young children (He et al., 1999; Massarella et al., 2000; Oo et al., 2003; Pope et al., 2005) to support their point that very young children have reduced carboxylesterase capacity and that this affects the pharmacokinetics through delayed hydrolysis. In fact, neither of these statements is supported by the references cited, and it is inaccurate to infer such conclusions from half-life data alone. Indeed, Oo et al. (2003) reported the apparent clearances of oseltamivir (per kilogram body weight) in younger children to be higher than in older children and concluded that carboxylesterase activity in this age group is efficient. Pope et al. (2005) also showed that the range of expression and activity of HCE1 in this age group is similar to that of adults.

In conclusion, whereas this study provides useful information concerning the activation of oseltamivir by HCE1, the data presented indicate that, at the clinical concentrations achieved with oseltamivir and clopidogrel, the likelihood of any significant metabolic interaction between the two compounds is remote.

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